PATENT COOPERATION TREATY

1 week extension allowed NLW 3.6.04

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	03.05.2004
Applicant's or agent's file reference SCB/58858001	**REPLY DUE** **within 1 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/00034	07.01.2003	07.01.2002

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
NORCHIP A/S et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07.05.2004

RECEIVED
30 APR 2004
BOULT WADE TENNANT

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-91 as originally filed

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

Sequence listing part of the description, pages:

1-67, filed with the letter of 02.05.2003,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3-5 (complete); 1, 2, 6-16 (all partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 3-5 (complete); 1, 2, 6-16 (all partially)

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 2, 6-16 (all partially) .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 2, 6-10 (all partially)
Inventive step (IS)	Claims	1, 2, 6-16 (all partially)
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

V. **Reasoned statement** (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

D1: WO 01 73135 A (MOLODYSKY EUGEN ;BIOSEARCH INTERNAT PTY LTD (AU); CORD JANET I (US) 4 October 2001 (2001-10-04)

D2: WO 99 29890 A (DIGENE CORP ;LORINCZ ATTILA T (US)) 17 June 1999

D3: LANHAM S ET AL: 'HPV detection and measurement of HPV 6, telomerase and survivin transcripts in colposcopy clinic patients' JOURNAL OF CLINICAL PATHOLOGY, LONDON, GB, vol. 54, no. 4, April 2001 (2001-04), pages 304-308.

D4: EP-A-0 662 518 (AMOCO CORP) 12 July 1995

D5: EP-A-0 373 352 (BEHRINGWERKE AG) 20 June 1990

D6: DE 44 31 174 A (DEUTSCHES KREBSFORSCH) 7 March 1996

D7: WO 94 26934 A (BROWN JANICE T ;BAXTER DIAGNOSTICS INC (US)) 24 November 1994

D8: SMITS H L ET AL: 'Application of the NASBA nucleic acid amplification method for the detection of human papillomavirus type 16 E6-E7 transcripts' JOURNAL OF VIROLOGICAL METHODS, AMSTERDAM, NL, vol. 54, no. 1, 1995, pages 75-81.

D9: CORNELISSEN M T E ET AL: 'UNIFORMITY OF THE SPLICING PATTERN OF THE E6/E7 TRANSCRIPTS IN HUMAN PAPILLOMAVIRUS TYPE 16-TRANSFORMED HUMAN FIBROBLASTS, HUMAN CERVICAL PREMALIGNANT LESIONS AND CARCINOMAS' JOURNAL OF GENERAL VIROLOGY, SOCIETY FOR GENERAL MICROBIOLOGY, READING, GB, vol. 71, no. PART 5, 1 May 1990, pages 1243-1246.

D10: MCNICOL PATRICIA ET AL: 'Expression of human papillomavirus type 16 E6-E7 open reading frame varies quantitatively in biopsy tissue from different grades of cervical intraepithelial neoplasia' JOURNAL OF CLINICAL MICROBIOLOGY, vol. 33, no. 5, 1995, pages 1169-1173.

D11: JEON SAEWHA ET AL: 'Integration of human papillomavirus type 16 DNA into the human genome leads to increased stability of E6 and E7 mRNAs: Implications for cervical carcinogenesis' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 5, 1995, pages 1654-1658.

2.2 NOVELTY (Art. 33(2) PCT)

2.2.1 D1 discloses an *in vitro* method of screening human subjects to assess their risk of developing cervical carcinoma (see Abstract and page 11, lines 20-30) which comprises the detection of E6 and L1 mRNA transcripts (see page 12, lines 1-8). The positive or negative result in the detection of said transcripts is used to score the risk of developing cervical carcinoma (page 14 and Tables 1-3). This document also explains how patients can be sorted in "risk categories" depending on the presence or absence of said transcripts (see page 14, lines 19-25), and includes the differentiation between high and low risk HPV typing depending on the mRNA detected (page 14, lines 7-12). The use of NASBA technique for detection is also disclosed (see page 13, lines 9-14).

2.2.2 D2 discloses an *in vitro* method of screening human subjects to assess their risk of developing cervical carcinoma (see Abstract: "to assess the progression of HPV infection from benign to malignant growth"; see also pages 1-3). The method comprises the detection of E6 and L1 mRNA transcripts (see page 7, line 30, to page 11, line 9). The results are used to score the risk of developing cervical carcinoma and to sort the patients in "risk categories" (pages 8-12; Table 1). The use of NASBA technique for detection is also disclosed (see page 13, line 21).

2.2.3 A similar method, with the same purpose and comprising the same steps, is described in D3.

2.2.4 Therefore, claims 1 and 2 are not novel.

2.2.5 D4 discloses an *in vitro* method of screening human subjects to assess their risk of developing cervical carcinoma (see Abstract: "prognosticating serious cervical neoplasias and cancers"; see also page 2, lines 20-26; page 3, lines 49-53: "risk of progression to serious dysplasia"; and page 4, line 1, to page 5, line 22). The method comprises screening the subject for expression of mRNA transcripts of the E6 gene of HPV (see page 2, line 27-38; page 5, line 34, to page 14, line 8). The step of quantitation of E6 mRNA is described as optional (see page 2, line 27; claims 8 and 9). The step of *categorizing* the results between "high risk" (E6 mRNA present) and "no detectable risk" (E6 mRNA

absent) for development of cervical carcinoma is considered implicit to the method of D4. This especially is evident in view of the passages cited above regarding the purpose of the method (pages 1-5).

2.2.6 D5 discloses an *in vitro* method of screening human subjects to assess their risk of developing cervical carcinoma (see Abstract: "...und so den Hinweis auf prämaligne oder maligne Zustände bzw. Läsionen"; page 2, lines 13-24: "korreliert wahrscheinlich mit dem malignen Potential"). The method comprises screening the subject for expression of mRNA transcripts of the E6 gene of HPV (see page 2, line 28, to page 6, line 3). As above, the step of categorizing the results between "high risk" (E6 mRNA present) and "no detectable risk" (E6 mRNA absent) for development of cervical carcinoma is considered implicit to the method of D5, especially in view of the passages cited regarding the purpose of the method (Abstract and page 2, lines 13-24).

2.2.7 D6 discloses an similar method of screening human subjects to assess their risk of developing cervical carcinoma (see page 2, lines 5-13: "im Rahmen der Krebsvorsorge und/oder Therapiekontrolle"; see also page 3, line 55, to page 4, line 37: "Beispiel: Nachweis von Zervix-Karzinom-spezifischer mRNA aus Blut"). The method comprises screening the subject for expression of mRNA transcripts of the E6 gene of HPV (see page 2, line 14, to page 4, line 37). Again the step of categorizing the results between "high risk" (E6 mRNA present) and "no detectable risk" (E6 mRNA absent) is considered implicit to the method of D6, since the E6 transcript is described as *tumor-specific*, in the context of cervical cancer (see page 2, line 14, and claim 1).

2.2.8 Documents D7 to D11 describe similar methods of detection of E6 transcripts in the context of diagnosis/prognosis of cervical carcinoma.

2.2.9 Therefore, the method of claim 6 is not novel.

2.2.10 Since premalignant and malignant cells are considered as having "abnormal cell changes", the method of claim 7 is not novel in view of D4-D11 (see above).

2.2.11 D4 discloses the use of cervical smears from human subjects previously identified as infected (see page 11, lines 20-25). Claim 8 is therefore not novel.

2.2.12 D9 discloses the use of samples from patients having a previous diagnosis of CIN lesions (page 1245, column 1), and D2 specifically mentions CIN-I lesions (page 10, line 23). Claim 9 is therefore not novel.

2.2.13 D5 discloses that the detection of E6 mRNA implies that the samples are scored as carrying integrated HPV (see page 2, line 16). Claim 10 is therefore not novel.

2.2.14 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1, 2 and 6-10 is not novel in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.3 INVENTIVE STEP (Art. 33(3) PCT)

2.3.1 Dependent claims 11-13 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step because consensus primers for L1, for example GP5, GP6 and their variants, and specific primers for high-risk HPV E6 were routinely used in the clinics for HPV detection at the time of priority of the present application. Multiple references to documents describing and using said primers can be found for example in D1 (page 6, line 17, to page 10, line 9) and D2 (page 15, lines 2-9). Sequences of such primers can also be found in D6 (column 6, line 41, to column 58, line 50). Therefore, the use of said primers does not appear to contribute an inventive step to the methods claimed.

2.3.2 Dependent claims 14 and 15 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step, because they fall under the scope of routine experimental design and optimization, and the skilled person would include these features in order to solve the problem posed without the involvement of an inventive step.

2.3.3 Primers suitable for use in amplification of L1 and E6 transcripts are implicitly disclosed in D1 when describing the methods for detection including PCR and the sequences to be detected (see page 12, line 4, to page 13, line 31).

Bringing these primers together in the form of a kit to carry out the method disclosed in D1 would be obvious to the person skilled in the art. Furthermore, examples of said primers can be found in most of the documents cited (v.g. D3, Table 1).

2.3.4 Thus, claims 11-16 are not considered inventive.

2.3.5 The present application does therefore not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claims 1, 2 and 6-16 does not involve an inventive step (Rule 65(1)(2) PCT).

2.4 FINAL REMARKS

2.4.1 In view of the prior art cited, it is clear that the association between certain types of HPV, their integration into the host cell genome, its influence in the malignant transformation process of cervical cells, and the strong transcriptional activity of the E6/E7 transcription unit upon integration are well known in the field since more than 12 years before the present priority date. Furthermore, due to the clinical relevance of this finding, the topic has been subject of intense research, and a high number of documents has been published disclosing results based on said finding and its utility as marker to diagnose cervical tumors. Said documents teach also the detection of other transcription products derived from the integrated HPV genome, including L1 (see above), alone or in combination with E6, and their relevance in the diagnosis of cervical cancer.

2.4.2 Considering this background, this IPEA fails to see in the present application any inventive contribution to the art. The applicant is hereby invited to point out the differences between the claimed methods and the prior art cited, and to explain why these differences involve an inventive step. It must be noted, however, that such differences cannot rely merely in a re-formulation of the purpose and/or steps of known methods (v.g., on a *new* wording of how the results of HPV mRNA detection leads to a risk assessment).

2.4.3 In order to facilitate the examination of the conformity of the amended

application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify all the amendments carried out, no matter whether they concern amendments by addition, replacement, deletion, or changes in the dependency structure, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

2.4.4 The applicant is requested to note that in accordance with Rule 66.4 (a) PCT the issuance of an additional Written Opinion (WO) is facultative. Moreover, as the final action in the PCT procedure is an International **Preliminary** Examination Report (IPER) and not a decision, a violation of the right to be heard cannot exist. The applicant can not therefore rely on obtaining a second WO before the IPER is issued and is requested to answer this first WO in a complete manner.